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Do clinical variables predict an abnormal EEG in patients with complex febrile seizures?

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Summary

Purpose: Febrile seizures are the commonest convulsive event in children younger than 5 years of age (incidence of 2–5%). Electroencephalography (EEG) is not indicated in the work up of simple febrile seizures. Information about its role in the assessment of complex febrile seizures (CFSs) is unclear and EEGs are frequently ordered. This study was designed to assess utility of clinical variables at presentation in predicting the likelihood of an abnormal EEG.
Methods: EEG requisitions, EEG reports, clinic charts and medical records over an 11-year period (1990–2001) were retrospectively reviewed. The relationship between clinical variables like age, timing of the EEG since CFS, family history of seizures, neurological assessment and EEG abnormalities was statistically analyzed.
Results: One hundred and seventy-five children were included in the study. Of these 39.43% had EEG abnormalities. Children with a normal EEG were younger than those with an abnormal EEG (mean age 15.72 months versus 19.75 months, $p < 0.05$). Using multivariate analysis, factors predictive of abnormal EEGs in children with CFS were; age >3 years ($p = 0.010$; 95% CI: 1.5–18.8), EEGs performed within 7 days ($p = 0.00$; 95% CI: 1.78–7.12) and an abnormal neurological exam ($p = 0.053$; 95% CI: 0.98–16.9). A family history of febrile seizures was more likely to be associated with a normal EEG ($p = 0.01$; 95% CI: 0.04–0.60).
Conclusions: Clinical variables at presentation can be used to screen children with CFS for whom an EEG is considered. This may lead to better use of resources. Whether abnormal EEG translates to future recurrences or epilepsy needs a prospective study.

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Introduction

Febrile seizures (FS) are the commonest convulsive event in children less than 5 years of age with an incidence of 2–5%.[1–3] A febrile seizure is defined as a seizure occurring between 3 months and 5 years of age, accompanied by fever, without evidence of intracranial infection or a defined cause. Children who have suffered a previous afebrile seizure are excluded.[4,7] Febrile seizures are classified as simple or complex depending on duration, presence of focal features during onset or evolution, and recurrence within 24 h. Complex febrile seizures (CFSs) are either focal, or prolonged (greater than 15 min), and/or recur within 24 h. CFS are associated with an increased (4.1%) risk of epilepsy in later years.[2] Approximately 20–30% of first febrile seizures and 41% of recurrent febrile seizures are complex.[3,5,6]

The American Academy of Pediatrics practice parameter on Febrile Seizures states that EEG should not be a part of routine investigation after a simple febrile seizure in neurologically normal children due to it's lack of ability in predicting recurrence risk or future epilepsy.[7,8] In contrast, the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society and The American Epilepsy Society recommend an EEG in the initial evaluation of the first afebrile seizure, as an abnormal EEG predicts recurrence.[10]

The precise role of EEG in evaluation of patients with CFS has not been established, however, it is not uncommon for both pediatricians and specialists to recommend EEGs on these patients.[9] Only two published studies to date have looked specifically at CFS and the role of EEG in its evaluation.[11,12] In a retrospective review of 33 neurologically normal patients with EEGs within 1 week of CFS, Maytal et al.[11] found none with abnormalities, while Yucel et al.[12] reported abnormalities in 71 of 159 children with CFS analyzed retrospectively over 7 years. In the latter group, 16 were noted to have abnormal EEG records in the first week. Out of 71 patients with abnormal EEG records, 51 were diagnosed with epilepsy on follow up. The purpose of this study was to independently validate these findings and examine the association between clinical variables at the time of an EEG evaluation for the first CFS, and the presence of EEG abnormalities.

Materials and methods

The University of Manitoba Heath Research Ethics Committee and the Children's Hospital Research Impact Committee approved this study. Personal Health Information Act guidelines were strictly maintained in data analysis.

All EEG requisitions at the Children's Hospital (12,500 in total) were retrospectively reviewed to identify those EEGs performed for the indication of seizures with fever over an 11-year period (January 1st 1990 to December 31st 2001). When more than one EEG had been performed, the initial record was evaluated. All patients meeting criteria of febrile seizures (age 3 month to 5 years, presence of fever, absence of intracranial infection, or a defined cause such as electrolyte imbalance) with an EEG performed at our laboratory were further analyzed. Occurrence of an afebrile seizure predating the febrile seizure was an exclusion criterion. From this cohort those patients fulfilling criteria for CFS (focal, duration of greater than 15 min, or >1 seizure in a 24 h period) were selected in the present study. Neurology clinic files, and hospital medical records were reviewed to confirm the inclusion criteria and the diagnosis of CFS. Details such as date of the first EEG, age at the time of seizure, neurological assessment, family history of epilepsy or febrile seizures, seizure semiology, EEG results and subsequent development of afebrile seizures (if any) were also noted whenever available. EEG patterns were categorized as normal or abnormal on the basis of: (a) abnormality in the background rhythms (slow waves, focal and/or generalized), and/or (b) the presence of interictal epileptiform activity (sharp waves, spikes, and/or spike wave complexes) or both. All EEG recordings included awake and sleep states and had been read by a pediatric neurologist.

Statistical analysis

The individual clinical variables associated with EEG abnormalities were analyzed using multivariate analyses. Continuous variables were analyzed using parametric (Student's *t*-test) while categorical variables were analyzed using non-parametric test (χ^2-analysis). All variables were included in logistic regression analysis. Statistical analysis was performed by the hospital medical statistician, using SAS (version 8.13).

Results

Two hundred and two patients had been coded with a diagnosis of CFS. After review of medical charts, 27 patients were excluded due to previous afebrile seizures ($n = 9$), CNS infection ($n = 4$), history consistent with simple, not complex, febrile seizure

($n = 5$) and incomplete information regarding the timing of CFS ($n = 9$). The data on remaining 175 patients were included in the final analysis. The mean age was 17.31 months. One hundred and fifty eight patients (90.29%; 95% CI: 85.90—94.67) were younger or equal to 3 years, and 17 (9.71%; 95% CI: 5.32—14.10) were older than 3 years. Children with abnormal EEGs ($n = 69$, 39.43%; 95% CI: 32.18—46.66) were older than those with a normal EEG ($n = 106$; mean ages 19.75 months versus 15.72 months, $p < 0.05$). Sixty-six EEGs (37.71%; 95% CI: 30.53—44.89) were performed within 7 days of CFS, and 109 (62.29%; 95% CI: 55.10—69.47) after 7 days of CFS. Abnormalities included; epileptiform patterns ($n = 28$, 40.58%; 95% CI: 28.99—52.17), background slowing ($n = 31$, 44.93%; 95% CI: 33.19—56.66), or both ($n = 10$, 14.49%; 95% CI: 6.18—22.79). A positive family history of seizure was present in 72 children (41.14%; 95% CI: 33.85—48.43), 47 for epilepsy (65.27%; 95% CI: 54.28—76.27) and 25 for febrile seizures (34.72%; 95% CI: 23.72—45.71). Seizure types were categorized as focal ($n = 37$, 21.14%; 95% CI: 15.09—27.19), focal secondarily generalized ($n = 13$, 7.43%; 95% CI: 3.54—11.31), generalized ($n = 122$, 69.71%; 95% CI: 62.9—76.52), and unknown ($n = 3$, 1.71%; 95% CI —0.20—3.63). An abnormal neurological assessment on these children with CFS (that varied over a range of definite abnormalities to more subtle findings elicited during neurological examination) was reported in 15 (8.57%; 95% CI: 4.42—12.72) children. The findings included; postictal hemiparesis (6), static encephalopathy (1), known developmental delay (5), abnormal plantar response (1), macrocrania (not documented if familial or not) (1) unsteady gait (1), and movement disorder (myoclonus) (1) (Table 1).

On univariate analysis variables significantly associated with abnormal EEG included age older than 3 years (OR = 4.25; $p = 0.006$), EEGs done within 7 days (OR = 3.8; $p = 0.0001$), abnormal neurological exam (OR = 4.84; $p < 0.005$), presence of a family history of febrile seizures (OR = 0.162; $p = 0.005$).

On multivariate analysis, timing of EEG less than or equal to 7 days (AOR 3.56, 95% CI: 1.78—7.12; $p = 0.003$), age greater than 3 years (AOR 5.32, 95% CI: 1.50—18.87; $p = 0.0009$) and abnormal neurological exam maintained a trend for a strong association with abnormal EEG (AOR 4.32, 95% CI: 1.02—18.3, $p = 0.047$). A positive family history for febrile seizures reduced the likelihood of finding EEG abnormalities (AOR 0.16, 95% CI: 0.04—0.60; $p = 0.01$) and therefore increased the likelihood of a normal EEG report (AOR 6.41, 95% CI: 1.67—24.39). Three of 15 children with abnormal neurological exam had a positive family history for febrile seizures, the remaining 12 children had a negative family history for febrile seizures; 9 of these 12 children had an abnormal EEG.

The conditional distribution of the EEG results with respect to the above predictive variables is presented in Table 2.

Table 1 Clinical variables and descriptors in the sample.

	N observations/total	Percentage
Age		
<Or = to 3 years	158/175	90.29
>3 years	17/175	9.71
Timing of EEG		
= Or <7 days after seizure	66/175	37.71
>7 days after seizure	109/175	62.29
Family history		
Negative	103/175	58.86
Positive	72/175	41.14
Types of positive family history		
Positive for epilepsy	47/72	65.28
Positive for febrile seizures	25/72	34.72
Seizure type		
Focal	37/175	21.14
Focal secondary generalized	13/175	7.43
Generalized	122/175	69.71
Unknown	3/175	1.71
Neurological exam		
Abnormal	15/175	8.57
Normal	160/175	91.43

Table 2 Conditional distribution of predictors of EEG results.

Predictors	E/SE (%)	N (%)	S (%)	Total (*n*)
Seizure type[a]				
Generalized	31 (25.4%)	75 (61.5%)	16 (13.1%)	122
Focal	6 (16.2%)	24 (64.9%)	7 (18.9%)	37
F2g	1 (7.7%)	4 (30.8%)	8 (61.5%)	13
Unknown	0 (0.0%)	3 (100%)	0 (0.0%)	3
Age[a]				
≤36 months	27 (17.1%)	101 (63.9%)	30 (19.0%)	158
>36 months	11 (64.7%)	5 (29.4%)	1 (5.9%)	17
Timing of EEG[a]				
>7 days after seizure	20 (18.3%)	79 (72.5%)	10 (9.2%)	109
≤7 days after seizure	18 (27.3%)	27 (40.9%)	21 (31.8%)	66
Neurological exam[b]				
Normal	31 (19.4%)	102 (63.8%)	27 (16.9%)	160
Abnormal	7 (46.7%)	4 (26.7%)	4 (26.7%)	15
Family history[b]				
No family hx	24 (23.3%)	56 (54.4%)	23 (22.3%)	103
Positive hx of epilepsy	0 (0.0%)	4 (100%)	0 (0.0%)	4
Positive hx of febrile seizure	3 (12.0%)	22 (88.0%)	0 (0.0%)	25
Positive hx of seizure	11 (25.6%)	24 (55.8%)	8 (18.6%)	43
History of seizures[c]				
One previous seizure	20 (22.5%)	52 (58.4%)	17 (19.1%)	89
>1 previous seizure	16 (23.5%)	41 (60.3%)	11 (16.2%)	68
Duration of seizure[c]				
≤15 min	15 (23.4%)	41 (64.1%)	8 (12.5%)	64
>15 min	17 (24.6%)	36 (52.2%)	16 (23.2%)	69

S: slowing; E: epileptiform; SE: slowing and epileptiform; N: normal; F2g: focal secondarily generalized; hx: history.
[a] p-value <0.01.
[b] p-value <0.05.
[c] p-value >0.10 (not significant) and are obtained by applying the χ^2-test to the predictors vs. EEG results.

Discussion

A review of published literature suggests that between 2 and 86% of EEGs are abnormal after febrile seizures.[11] This variation can be attributed to differences in criteria used in subject selection by different authors, varying definitions of EEG abnormalities, and relationship of age, maturity, and timing since ictus to EEG findings. Although the topic of febrile seizures is widely studied, there are only two publications that are specifically and exclusively related to the topic of CFS[11,12] and look closely at the value of early EEG in work up of these patients. Since CFS is associated with increased risk of future epilepsy,[2] EEGs are frequently ordered. Our study is the first to specifically examine the effect of various clinical variables on the EEG results to strengthen or refute the existing practice.

The timing of the EEG post-seizure has been shown to be an important variable in determining the presence of epileptiform abnormalities. It is rare for epileptiform abnormalities to be reported within 7 days of FS.[13] However, slowing is found to be more prevalent in the early post-ictal period after FS.[11,16] Similar findings have been reported in other studies.[14,15] The incidence of paroxysmal abnormalities on EEG in neurologically normal children within a week of CFS was 0% in a study by Maytal et al.,[11] with a calculated true rate of abnormalities of 8.6% or less. In another study by Yucel et al.[12] 22.5% of abnormal EEGs (16 of 71) occurred within 6 days of CFS. On the basis of these previous studies we analyzed the EEGs by categorizing them as having been performed within or after 7 days.

Our results show that children with CFS are approximately 3.5 times more likely to display an abnormal EEG within 7 days post-ictus in comparison to children with CFS where the EEG was performed beyond the 7-day period post ictus. In the former group, 27.3% (18) had epileptiform abnormalities, and 31.8% (21) showed slowing. When EEGs were performed beyond 7 days post-ictus, 18.3% (20) showed epileptiform activity while 9.2% (10) showed slowing ($p < 0.0005$). Slowing of background

rhythms has also been reported in other studies; however in our study, the proportion of EEGs with epileptiform abnormalities was higher when the EEG was performed within 7 days of the ictus. This is an unexpected finding compared to previous reports[11,13,16] and lower than Yucel et al.'s[12] study where 16 out of 27 patients had epileptiform EEGs (59.3%) within 6 days of CFS. This result may be attributed to our inclusion criteria, where the emphasis was placed on the diagnosis of CFS without prescreening for a normal neurological exam or normal development; in contrast to other studies where neurologically normal children were studied.[11,12] Other confounders that could have contributed to the above findings may be the effect of viral infections on EEG[21] or the transient changes that have been described in EEGs between days 3 and 8 after a febrile seizure.[22] We were unable to validate these findings either due to incomplete information or small numbers. For example out of the 69 abnormal EEGs in our cohort, 39 were done on or before the seventh day (56.5%), of these, 14 patients had follow up EEGs (35.9%) and 3 out of the 14 were abnormal (21.42%).

The age of the child at the time of the first complex febrile seizure has also been shown to influence EEG findings. Detection of epileptiform patterns is seldom seen in children with FS aged less than 3 years.[17] This finding is in keeping with an age dependent effect of a linear trend for the detection of higher rates of epileptiform patterns with increasing age.[8,16,18–20] The results of our analysis support a similar conclusion.

An abnormal bedside neurological exam in children with CFS is a predictive variable of the likelihood of an abnormal EEG, as patients with abnormal neurological exams are approximately four times more likely to have abnormal EEG results. This effect was noted in the univariate analysis ($p = 0.005$) but with decreased statistical significance with multivariate analysis although a trend was maintained ($p = 0.047$). It is possible that the small numbers of patients with abnormal examination ($n = 15$) in this study diluted the effect on multivariate analysis. This finding therefore may still retain clinical relevance and merits a second look, as another study has drawn similar conclusion.[16]

We found that patients with a positive family history of febrile seizures showed a lower proportion of epileptiform abnormalities, in comparison to those children without a positive family history of febrile seizures, the latter group displayed a six times greater likelihood of abnormalities on their EEG. This effect may be attributed to the presence of a positive family history of febrile seizures being a predictor for recurrences of febrile seizures only and not epilepsy.

Our study carries the usual methodological drawbacks of a retrospective study; but taking into account the sample size and the careful attention to selection criteria, we believe that the study is sufficiently robust to give the results clinical and statistical validity.

While the EEG is a sensitive test for determination of abnormalities in the electrical activity of the brain, its value in the clinical practice of evaluating seizures is largely dependent on the finding of paroxysmal epileptiform patterns or slowing in background rhythms.[10] In Yucel's study[12] out of 71 patients with abnormal EEG, 51 were later diagnosed with epilepsy. We suggest that the following clinical variables: (a) the absence of a family history of febrile seizures, (b) abnormal neurological examination, (c) age greater than 3 years and (d) timing of the recording from ictus — when within 7 days, significantly influence the likelihood of finding abnormalities on the EEG. We speculate that finding an EEG abnormality may result in closer clinical follow up to monitor for recurrent afebrile seizures; but are limited by our study design in making any meaningful conclusions as to whether an abnormal EEG may have changed or influenced clinical decisions in our study cohort.

Furthermore we are unable to comment on the relationship of the abnormal epileptiform patterns found on EEG in children with CFS and the risks of recurrence or epilepsy in later childhood. The above issues, however, underscore the need for a planned prospective study for the evaluation of CFS.

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